TEMPERATURE
2023, VOL. 10, NO. 1, 35–49
https://doi.org/10.1080/23328940.2021.2017735

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PRIORITY REVIEW

Capsaicin and cancer: Guilty as charged or innocent until proven guilty?

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ABSTRACT

With an estimated 2 billion chili pepper connoisseurs worldwide, the human exposure to capsaicin is enormous. Therefore, the question whether nutritional capsaicin is a cancer causing or cancer preventive agent is of utmost importance.

The gamut of human epidemiology studies suggests that capsaicin in modest, "restaurant-like" doses is not only safe to eat, but it may even provide health benefits, such as lower cancer-related death rate. Very "hot" food is, however, probably better avoided.

Importantly, no increased cancer risk was reported in patients following topical (skin or intravesical) capsaicin therapy.

Aberrant capsaicin receptor TRPV1 expression was noted in various cancers with potential implications for cancer therapy, diagnosis and prognostication. Indeed, capsaicin can kill cancer cells by a combination of on- and off-target mechanisms, though it remains unclear if this can be exploited for therapeutic purposes.

The literature on capsaicin and cancer is vast and controversial. This review aims to find answers to questions that are relevant for our daily life and medical practice.

ARTICLE HISTORY
Received 2 October 2021
Revised 18 November 2021
Accepted 9 December 2021

KEYWORDS
Capsaicin; cancer; resiniferatoxin; nutraceutical; prevention; neuroimmune regulation

Introduction

Capsaicin is responsible for the piquancy of hot chili peppers. Connoisseurs of hot spicy food know the predominant pharmacological effects of capsaicin from personal experience. Capsaicin causes a hot, burning sensation in the oral mucosa that disappears upon repeated exposure: this unique action was termed "capsaicin desensitization" by Nicholas (Miklós) Jancsó who was the first to describe this phenomenon in the 1940ies [1]. Capsaicin also affects thermoregulation. Indeed, many people experience profuse perspiration, known as "gustatory sweating," after eating a spicy meal. János Szolcsányi, whose memory this Special Issue is dedicated to, made important contributions to our understanding of the capsaicin effects on thermoregulation [2].

Since chili plants use capsaicin as a deterrent to protect themselves against herbivores [3], it remains a puzzle why the same "hot" sensation which is unpalatable to squirrels, deer and other animals is found pleasurable by so many men [4]. With an estimated quarter of the World's population eating hot pepper on a daily basis, the dietary human exposure to capsaicin is enormous. The global hot pepper market value in 2018 reached 4.1 billion USD, with 166 K tonnes Vietnam being the largest producer. In addition, millions of people with chronic pain use over-the-counter (OTC) capsaicin creams (0.025% and 0.075%) regularly for pain relief [5,6]. Therefore, the question whether capsaicin can cause cancer (or, conversely, protect against it) in man is of utmost importance.

Perhaps not surprisingly, the literature on dietary capsaicin and cancer is peppered with conflicting reports, with some studies linking human capsaicin consumption to gastric cancer [7–9] whereas others promoting dietary capsaicin for chemoprevention [10]. Unfortunately, animal experiments are not less confusing. For example, in the rat DMH (1,2-dimethylhydrazine) model of colon carcinogenesis, dietary capsaicin was reported to promote [11], or, conversely, inhibit [12] tumor formation.

There are exhaustive and comprehensive reviews on capsaicin and cancer, covering all aspects from molecular carcinogenesis [13–15] to cancer pain in animal models [16] and cancer

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patients [17]. In these reviews, capsaicin is often referred to as a "double-edged sword" [18]. If so, will this sword harm us or protect us? Or maybe it is not a sword at all, but a harmless straw?

This admittedly subjective review aims to find an answer to these important questions.

Culinary capsaicin and gastric cancer: Human epidemiology

The highest per capita hot pepper consumption, 15 kg per person, was reported in Mexico [19]. Since peppers differ a lot in their "hotness" (that is, in their capsaicin content), it is difficult, if not impossible, to translate these "kg per person pepper consumption" data to dietary capsaicin exposure. However, considering that 1/3 of the Mexican pepper production is of the jalapeño chili variety (which may contain up to 6 g capsaicin per 100 g pepper), the average Mexican by adding 41 g hot pepper to his daily meal may consume as much as 2,400 mg capsaicin [20]. By comparison, the generic chili sauce in Germany contains 5,000 mg/kg capsaicin, and authorities consider 300 mg capsaicin in one meal as standard of traditional spicy cuisine [21].

Gastric cancer represents the 3rd highest cause of death by cancer in Mexico in people older than 20 years [22]. In the 75 years or older age group, the incidence of gastric cancer is 47 patients per 100,000 males [22]. Only an estimated 5–10% of gastric cancer cases are caused by inherited gene defects [23]. That is, most gastric cancers are not hereditary in origin and modifiable life-style factors like smoking, alcohol consumption or eating spicy meals can have an important impact on their development [23]. Given the popularity of eating hot, spicy meals in Mexico, it was a reasonable assumption that capsaicin may represent a risk factor for developing stomach cancer [7].

To evaluate this risk, population-based case control studies were conducted in patients with histologically proven gastric adenocarcinoma. The study participants filled out a dietary questionnaire adapted for the typical Mexican diet. Odds ratios were calculated for chili consumption (low, moderate, and high by self-reporting), and adjusted for variables like age, gender, calories intake, and cigarette smoking. In 1994, López-Carillo and colleagues found an odds ratio of 5.49 (95% confidence interval) for developing gastric cancer for chili pepper consumers compared to non-consumers [7]. Subsequently, Trujillo Rivera *et al* [24] defined the "at risk" dose of capsaicin as higher than 29.9 mg per day (this is only 1/10th of the capsaicin dose found in a "standard" spicy meal!).

A recent meta-analysis of 16 studies from different regions of the World found a pooled odds ratio of 1.51 for gastric cancer comparing chili eaters and non-eaters with striking geographical differences [9]. For example, Chinese [25] and Indian [26] case control studies reported increased odds ratios similar to that described in Mexico, whereas studies in Venezuela [27], Uruguay [28] and the Netherlands [29], by contrast, found decreased hazard ratios for stomach cancer in chili eaters compared to non-eaters, indicating protection.

These discrepant results (increased risk versus protection) highlight the inherent problems of these studies. For instance, chili peppers vary a lot in their capsaicin content and it is possible that Mexicans and Venezuelans prefer different (hotter versus milder) chili varieties; that is, the same daily pepper consumption may mean very different capsaicin exposures. "Hot" is also quite subjective: a Scandinavian may describe a meal as "hot," although the same meal is perceived as bland by a Mexican. Moreover, different ethnic groups may differ both in genetic susceptibility and dietary preferences. For example, diets may include nutrients which protect against cancer or, conversely, promote tumorigenesis. Therefore, we may not be comparing apples to apples and oranges to oranges. Indeed, in the US, Mexican-Americans on western diet still have a higher incidence of gastric carcinoma than their white compatriots [30]. To explain this paradox, it was postulated that it is not capsaicin *per se*, but the combination of high capsaicin consumption, H. pylori colonization, and IL1B-31 C > T genotype (which is more prevalent in Mexicans) that increases the risk for gastric cancer [31,32].

To add to the confusion, a large population-based study involving 16,179 American adults followed for 18.9 years reported a mortality of 21.6% among those who eat chili regularly compared to

33.6% mortality among those who do not [33]. This translates to a hazard ratio of 0.87, indicating a smaller risk of dying earlier for chili-eaters.

A similar health benefit (a 14% reduction in mortality) for regular spicy food consumption was found by analyzing the China Kadoorie Biobank data in which almost half million Chinese were enrolled [34]. Importantly, the chili-eater group also showed lower cancer-related death rate. Indeed, chili may be "too hot for cancer to handle" [35].

Dietary capsaicin is passed from the stomach to the intestines where it is either absorbed or stays in the stool. As the Hungarian saying goes, "hot pepper bites twice." Surprisingly, so far no published study has examined the effect of capsaicin consumption on developing colorectal carcinoma (although, as we will see below, the literature on capsaicin and experimental colon cancer is substantial).

Dietary capsaicin and cancer: Animal experiments

The German Bundesinstitut für Risikobewertung (the equivalent of the Federal Office of Consumer Protection and Food Safety) regards a consumption quantity of 5 mg capsaicin per kg body weight (that is, 300 mg by a 60 kg adult) as a "safe" dose not to be exceeded when preparing a meal with hot chili peppers [21]. To mimic this exposure, chili extract (corresponding to a capsaicin dose of 1.25 mg/kg) was included in the drinking water of BALB/c mice for the duration of the study (16 month): in these animals, no difference in stomach tumors (papillomas and/or carcinomas) was observed compared to controls [36]. Capsaicin, however, did promote stomach carcinogenesis in animals initiated with methyl-(acetoxymethyl)nitrosamine at a dose of 2 mg/kg [36]. Of note, for this study authors purchased chili peppers at a local market in Bombay (now Mumbai) that raises concerns about the purity of preparation.

In other studies, pure capsaicin was used. B6C3F1 mice were fed chow containing 0.25% capsaicin for 79 weeks [37]. On week 83, the animals were killed and autopsied: no difference in tumors was found compared to controls [37]. By contrast, more Swiss mice on life-long capsaicin diet (0.03125%) developed more cecum adenomas than controls: 22% versus 8% [38].

Among chemically-induced rodent models of colon cancer, probably 1,2-dimethylhydrazine (DMH) is the most frequently used. Confusingly, in the very same model, capsaicin was reported to promote [11] or block [12] colon carcinogenesis or leave it unchanged [39].

Capsaicin is metabolized in the liver. In an early study, adding chili pepper (0.5%) to high-fat diet for 6 months exacerbated the liver damage that fat causes in rabbits [40]. Many animals developed cirrhosis, a known precursor to hepatocellular carcinoma in man. [Parenthetically, dietary capsaicin suppressed liver fibrosis in Balb/c mice following bile duct ligation [41].

Furthermore, rats developed liver tumors when eating hot pepper on a daily basis [42]. Again, these early studies employed chili peppers from local markets. These peppers are often contaminated by natural toxins produced by fungi. For example, almost a 90% of pepper samples collected at local markets in Iran were found to contain aflatoxin [43], a known liver carcinogen. Therefore, the possibility that in these early pepper feeding studies a contaminant (and not capsaicin) caused cancer cannot be ruled out.

In a two-stage hepatocarcinogenesis rat model (diethylnitrosamine/phenobarbital), daily intake of pure capsaicin (0.02%, that resembles moderate human consumption) decreased the number of preneoplastic liver lesions, indicative of chemoprevention [44]. This finding implies a protective role of TRPV1 activation against hepatocellular carcinoma. Indeed, genetic inactivation of *Trpv1* (TRPV1 null mice) resulted in increased metastatic burden in a murine model of liver cancer [45].

Dietary capsaicin (5 mg/kg/day via gavage) blocked the formation of nitrosomethylurea-induced mammary tumors in rats [46]. In a similar dose (5 mg/kg three times a week), dietary capsaicin also decreased the metastatic tumor burden in TRAMP mice [47], a transgenic prostate cancer model.

These recent animal studies are in agreement with the reduced cancer-specific mortality in people who consume capsaicin on a daily basis [33,34].

Dietary capsaicin as nutraceutical in cancer patients

As discussed above, there is good experimental evidence that capsaicin can protect against varies tumors in animal models. By contrast, the concept that dietary capsaicin may be beneficial in cancer patients is either speculative or based on anecdotal evidence only. For example, in a patient with advanced prostate cancer, the prostate-specific antigen (PSA) doubling time (a serum marker of tumor progression) decelerated and the PSA level eventually stabilized when the patient decided to consume 2.5 ml habaneros chili sauce twice a week [48]. Possibly inspired by this report, capsaicin (along with curcumin) was promoted as a food complement for men with advanced castration-resistant prostate cancer [49].

In patients with pancreatic ductal adenocarcinoma, capsaicin was proposed to complement gemcitabine chemotherapy [50]. Furthermore, it was speculated that dietary capsaicin may possess a chemopreventive potential in patients with high-risk for developing pancreas cancer [51]. It can be also speculated based on xenograft studies that capsaicin could complement cisplatin in osteosarcoma patients [52], and sorafenib in patients with hepatocellular carcinoma [53]. These concepts are yet to be tested in the clinic.

Topical capsaicin in pharmacotherapy: A risk for cancer?

Capsaicin is unique among naturally occurring irritants in that the initial excitation that it evokes in sensory neurons (perceived as burning pain) is followed by a lasting refractory state, traditionally termed "desensitization" [1], during which these neurons remain "silent," unresponsive to various stimuli unrelated to capsaicin [54]. The molecular mechanisms of capsaicin actions are beyond the scope of this review (interested readers are to referred to [55,56]). Here is suffices to mention that capsaicin evokes its specific sensory neuronal actions by activating the TRPV1 receptor (Transient Receptor Potential Vanilloid-1, formerly known as the vanilloid VR1 receptor) [57]. Importantly, TRPV1 is also gated by noxious heat [57]. This explains why capsaicin is evoking a burning sensation. The seminal discovery of heat sensation by TRP channels earned the 2021 Nobel Prize in Medicine and Physiology to Davis Julius. Of note, TRPV1 is the founding member of the family of temperature-sensitive TRP channels, the so-called "thermoTRPs" [58]: combined, these channels cover a broad temperature range from noxious heat to freezing cold.

The molecular mechanisms that underlie capsaicin desensitization are still poorly understood [56]. The therapeutic potential of capsaicin desensitization is, however, well-documented in patients with medical conditions like chronic neuropathic pain [59] or neurogenic bladder [60].

For pain relief, capsaicin can be applied to the skin either in low-concentration (0.025% or 0.0075% capsaicin) creams [5,6] or high-concentration (8% capsaicin) patches [61,62]. Of note, capsaicin can also be administered in site-specific injections, for example into the knee joint of patients with pain secondary to osteoarthritis [63].

In 2012, the combined sales of Qutenza (8% capsaicin patch) were estimated at 7.8 million USD [64]. In clinical trials, a total of 2,848 patients received Qutenza [65]. In the US (that accounts for approximately 40% of the Qutenza market), pharmacies sell Qutenza for around 900 USD per kit. Assuming one patient per one kit, in the US 3,600 patients are exposed to high-dose capsaicin annually; importantly, so far no case of skin cancer developing in the treated skin surfaces of these patients has been reported. In keeping with this, biopsies taken from the skin of capsaicin-treated volunteers showed no evidence of epidermal dysplasia [66].

Capsaicin (and its ultrapotent analog, resiniferatoxin [56]) can be administed *via* a catheter into the bladder of patients with neurogenic bladder/destrusor instability [60,67]. In these patients, resiniferatoxin was reported to increase the bladder volume at which the first urge to void occurs [67,68]. In some incontinent patients, capsaicin may even restore continence [67]. In biopsies obtained from the bladder mucosa of patients undergoing capsaicin therapy, no pathologic changes were described in the urothelium [69]. Therefore, in the human skin and urinary bladder topical capsaicin was deemed safe for long-term

use. Indeed, carcinogenesis is not listed as a possible adverse effect in the documents that accompany capsaicin preparations.

Topical capsaicin in the mouse skin: Oncogenic, but off-target?

In the '70ies, the mouse ear erythema test was broadly used as a surrogate bioassay to discover putative tumor promoting agents in natural sources. In fact, resiniferatoxin, a phorbol-related diterpene analog of capsaicin, was isolated from the latex of *Euphorbia resinifera* as a putative tumor promoter based on its extraordinary irritancy in the mouse skin [70]. In a two-stage carcinogenesis model, resiniferatoxin did not promote the formation of tumors in the skin of NMRI mice after 7,12-dimethylbenzanthracene (DMBA) initiation [71], nor did it affect the phorbol 12-myristate 13-acetate (PMA)-induced epidermal hyperplasia [72], though it did block the inflammatory response to PMA [72,73]. In CD1 mice, resiniferatoxin applied to the shaved back skin caused no skin tumors during the lifetime of the animals (Blumberg and Szallasi, unpublished observation).

In the shaved back skin of ICR mice, capsaicin treatment (a single topical application of 10 μmol) followed by bi-weekly administration of 12-O-tetradecanoylphorbol-13-acetate (TPA), a known tumor promoter, resulted in no increase in the number of skin tumors compared to solvent controls [74]. On the contrary, capsaicin ameliorated papilloma formation when co-applied with TPA [75]. In keeping with this effect, capsaicin was found to suppress the TPA-induced epidermal activation of NF-κB [75]. Furthermore, similar to resiniferatoxin, capsaicin failed to promote DMBA-induced mouse skin carcinogenesis [76].

Importantly, these negative capsaicin results were replicated in the transgenic Tg.AC mouse [77] that provides a sensitive assay for oncogenic agents.

Another study, however, reported exactly the opposite results: capsaicin applied to the shaved back skin of DMBA-initiated and TPA-promoted mice accelerated tumor growth and produced more and larger skin tumor compared to solvent controls [78]. Furthermore, capsaicin exacerbated the TPA-induced epidermal hyperplasia [73].

A third study [79] pointed out the crucial problem with these animal experiments. Although capsaicin is best recognized as the archetypical agonist of the vanilloid receptor TRPV1 [56,57], it is known to interfere with a multitude of other receptors and enzymes [55,56,80], and it may even influence membrane fluidity [81]. If the co-carcinogenic action of capsaicin is on-target, that is, mediated by TRPV1, it should be absent in TRPV1 null animals. This is not the case: in this study, no difference was noted between TRPV1 null and wild-type animals in the number and size of skin tumors [79].

Taken together, these findings imply that the co-carcinogenic action of capsaicin is off-target (i.e. not mediated by TRPV1), and the discrepant results may be attributed to mouse strain-related differences in nonspecific capsaicin targets. One can only hope that the molecular mechanism that underlies the co-carcinogenic action of capsaicin in the skin of certain mouse strains is not involved in the development of human skin cancers. This hope has some support. In restaurant workers who handle large amounts of chili peppers severe skin irritation (so-called "Hunan hand") was reported, but no cancers [82].

TRPV1 antagonists and cancer

If the oncogenic action of capsaicin is off-target, TRPV1 antagonists should not pose a risk for carcinogenesis. The molecular cloning of TRPV1 in 1997 [57] launched a concentrated effort by pharma to develop clinically useful antagonists [83]. Indeed, a number of potent, small molecule TRPV1 antagonists progressed into Phase I clinical trials with record speed [83]. The side-effects (e.g. hyperthermia and impaired noxious heat sensation) that plagued the use of these compounds in the clinics are beyond the scope of the review [83,84]; here it suffices to mention that no concern was raised for carcinogenesis.

In the published literature, there are only three reports on the oncogenic potential of TRPV1 antagonists in the mouse skin. Two of these papers tested three TRPV1 antagonists (AMG9810, SB-705498 and PAC-14028) and found no effect on keratinocyte proliferation and/or skin tumor development

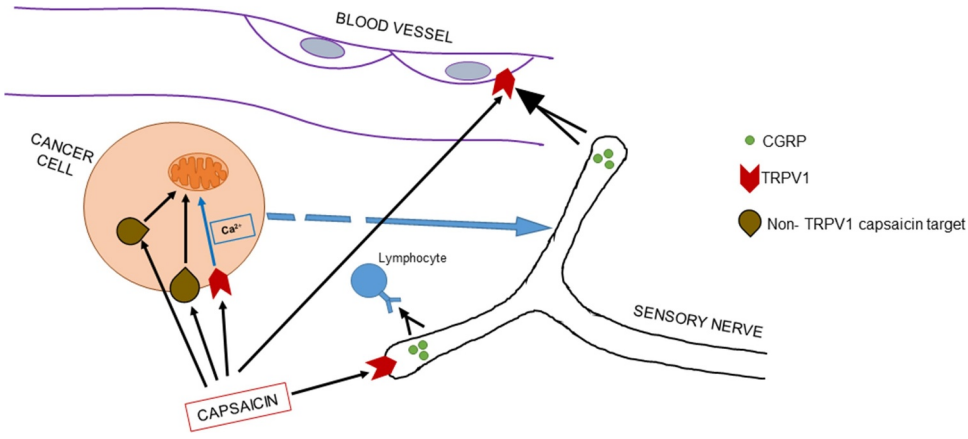

Figure 1. Capsaicin can influence tumor growth both directly (through TRPV1 expressed on cancer cells or via off-target, not TRPV1-mediated mechanisms) and indirectly (by initiating the biochemical cascade collectively known as neurogenic inflammation).TRPV1 is a nonselective Ca^{2+} channel. When activated by capsaicin, TRPV1 allows large amounts of Ca^{2+} to flow into the tumor cell: this may trigger apoptosis. Capsaicin may also damage tumor cells by perturbing membrane fluidity or directly activating molecular pathways of apoptosis. Capsaicin can also alter the interaction between the tumor and its microenvironment. TRPV1 is highly expressed on sensory nerve endings. When activated by capsaicin, these nerves release large amounts of sensory neuropeptides, such as calcitonin gene-related peptide (CGRP), in the tumor microenvironment. CGRP may attract immune cells and/or influence blood flow. This is a two-way road since the tumor may induce aberrant branching of the sensory nerves. Figure courtesy of Krisztina Pohóczky (University of Pécs, Hungary).

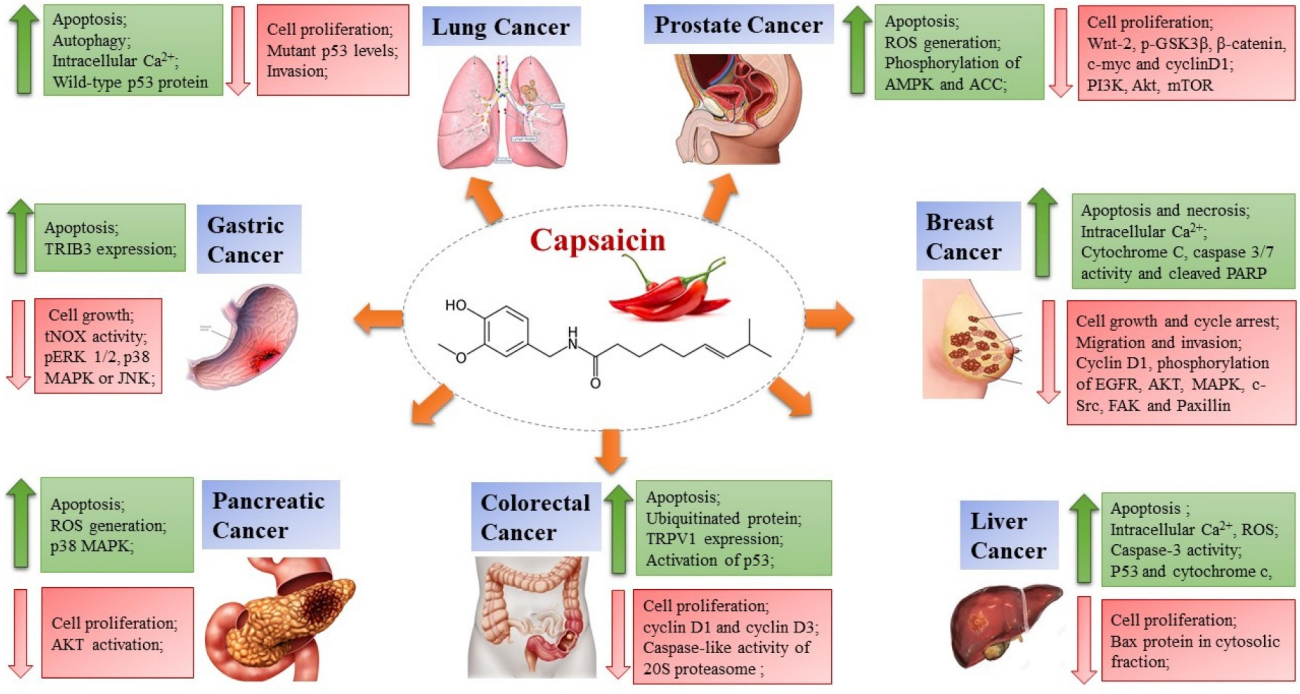

Figure 2. The diverse off-target molecular mechanisms by which capsaicin can block the growth of various tumors and/or kill cancer cells. Reproduced with permission of The Royal Society of Chemistry from [89].

[85,86]. The third report, however, described more skin tumors following AMG9810 administration [87]. It is not clear from the study if this effect was on- or off-target. It might be informative to repeat this experiment in TRPV1 null mice.

Capsaicin: A potent new weapon to kill cancer cells?

A complex interaction is emerging among capsaicin, sensory afferents and cancer cells (Figure 1). A recent comprehensive review lists all the cancer

cells in which capsaicin has been reported to induce apoptosis *in vitro* [88]: these cells range from breast and bladder carcinoma through melanoma to osteosarcoma and glioblastoma (Figure 2). The molecular mechanisms that may underlie capsaicin-induced tumor cell apoptosis (Figure 2) were reviewed elsewhere [14,89]. Although, albeit at low levels, many of these cell lines express TRPV1 (Table 1), the cancer-killing action of capsaicin appears to be predominantly off-target [14,89]. For example, capsaicin blocks the proliferation and invasion of BC6823 gastric carcinoma cells by directly inhibiting lysine-specific histone demethylase-1A (KDM1A/LSD1$_c$) with an IC_{50} (0.6 μM) [90] which is similar to the concentration at which capsaicin activates TRPV1 [91]. Furthermore, in nasopharyngeal carcinoma cells capsaicin blocks MKK3-induced p38 activation by directly interacting at p38 [92], and in breast [93] and prostate cancer cells [94] it targets the Wnt/β-catenin pathway.

Table 1. *TRPV1* gene expression in human cancers relative to normal tissue counterpart (data are from [88]). Changes in TRPV1 mRNA and/or protein (TRPV1-like ir) levels in cancers and their proposed significance.

Cancer	relative *TRPV1* gene expression (cancer/normal)	change in TRPV1 expression	significance
bladder	1.319	↓/↓↓ (TRPV1-like ir)	correlates with differentiation [95]
breast	0.796	↑↑↑ (mRNA)	correlates with differentiation [96]
cervix	1.283	aberrant TRPV1 protein expression	potential therapeutic target [97]
colon	0.968	↑ (TRPV1-like ir)	? [98]
head-and-neck	1.597	↑↑	potential therapeutic target [130,131]
kidney (clear cell)	0.896	↓↓↓	correlates with nuclear (Fuhrman) grade [99]
liver	0.958	↑↑	heralds good prognosis [45,100]
lung (adenocc)	1.955	N.D.	
prostate	0.970	↑ (TRPV1-like ir)	? [101]
thyroid	1.253	↑	? [102]
uterus	1.171	↑	? [103]

This is a problem. In addition to its hypothermic action [104], systemic capsaicin evokes a number of respiratory and cardiovascular reflex responses that may prove fatal [105]. In rodents, the dose of capsaicin that can be administered by subcutaneous injection is limited by respiratory depression [106]. Therefore, it might be difficult, if not impossible, to administer capsaicin at sufficiently high doses to kill cancer cells without causing unacceptable side-effects. The only exceptions may be cancers, like skin or oral carcinoma, that could amenable to topical capsaicin therapy [107].

Capsaicin-sensitive sensory afferents: An important role in neuroimmune regulation of carcinogenesis?

The neuroimmune regulation of carcinogenesis is subject to excellent recent reviews [108–110]. The diverse roles that capsaicin-sensitive afferents are thought play in neuroimmune interactions are detailed elsewhere [111]. Briefly, capsaicin-sensitive afferents are sites of release for a number of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), that initiate the biochemical cascade known as neurogenic inflammation (Figure 1) [54–56]. Neurogenic inflammation has been implicated in the pathogenesis of various human diseases, including cancer [112]. Sensory neuropeptides also play a role in the regulation of local blood flow [56] that, in turn, may influence cancer growth and metastasis (Figure 3). Last, these neuropeptides may exert trophic actions on tumor cells and/or change their phenotype, rendering the cancer more or less aggressive [113,114] .

Capsaicin-sensitive neurons can be defunctionalized or ablated by high-dose TRPV1 agonist (capsaicin or resiniferatoxin) treatment [55,56], and the participation of these neuronal pathways in oncogenesis can be explored in animals with non-functioning nerves. It should be noted upfront that so far no spontaneous tumor formation has been reported in capsaicin-treated rodents.

There is a growing body of evidence that an important cross-talk exists between the tumor and the capsaicin-sensitive sensory neurons in the tumor microenvironment [114,115]. An example of this phenomenon is breast cancer that can cause aberrant branching of capsaicin-sensitive

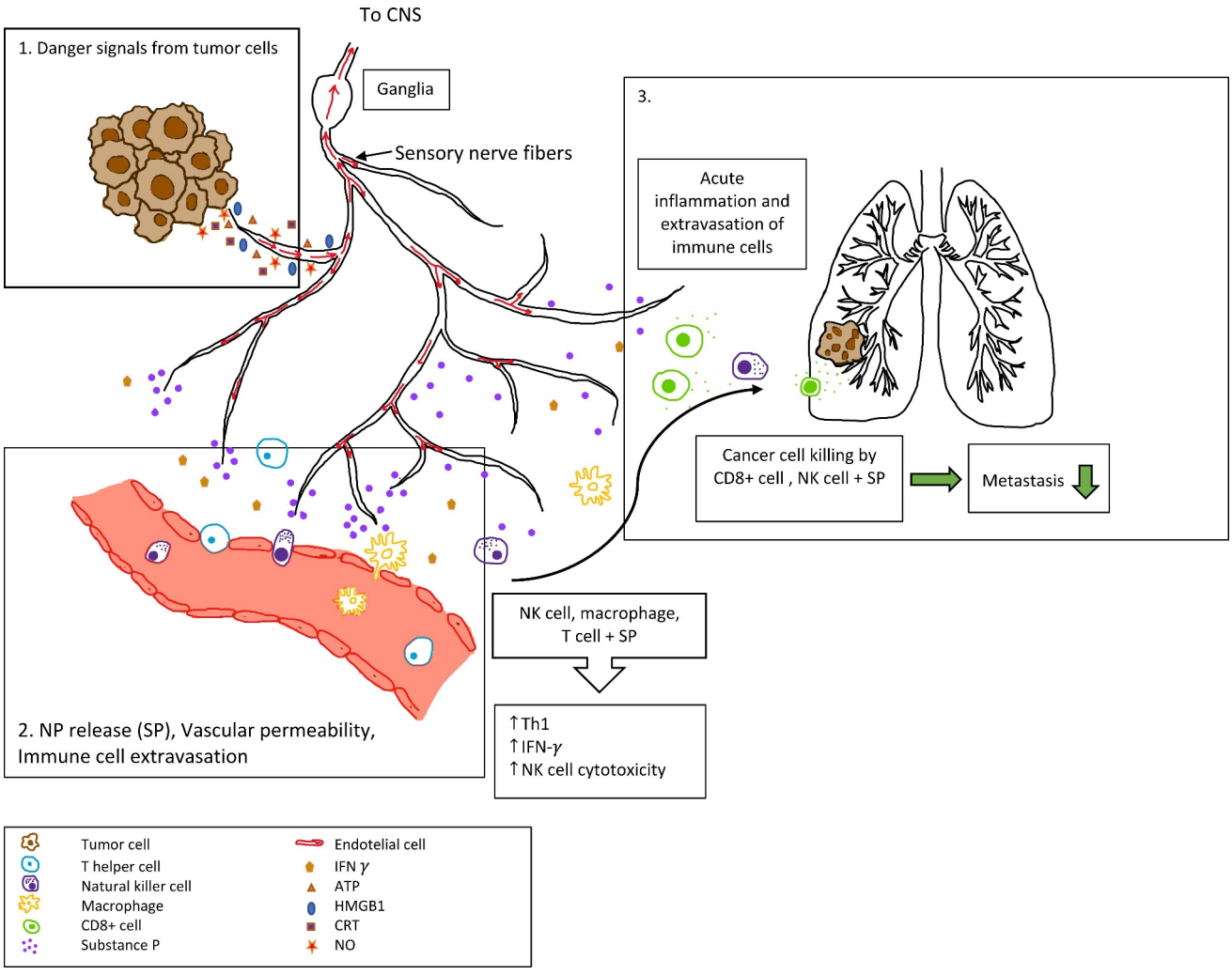

Figure 3. The neuro-immune axis that controls the metastatic potential of triple negative breast cancer. Capsaicin-sensitive afferents react to "danger signals" from tumor cells by releasing vasoactive substances like substance P. Immune cells (NK cells, macrophages and cytotoxic T- cells) that are part of this neurogenic inflammatory response attack and kill the circulating cancer cells. Chemical ablation by capsaicin of sensitive nerves accelerates metastasis formation in the lung. According to this model, the controlled activation of capsaicin-sensitive nerves could protect the patient from metastatic disease.Figure courtesy of Prof. Nuray Erin (Akdeniz University, Turkey).

afferents [116] that, in return, may alter the phenotype of cancer cells [113]. In the triple negative 4T1 orthotopic mouse model of breast cancer, chemical ablation by capsaicin of sensitive nerves accelerated metastasis formation in the lung and heart (Figure 3) [117]. In this model, resiniferatoxin treatment increased early tumor growth *via* vascular leakage, but the difference in tumor size disappeared by day 7 [118].

If the absence of capsaicin-sensitive afferents in the tumor microenvironment increases the metastatic potential of cancer cells [117], the activation of these nerves should have the opposite effect (Figure 3). Indeed, it was proposed that controlled activation of capsaicin-sensitive nerves could protect the patient from metastatic disease [115]. Unfortunately, the author did not explain how to activate these afferents by TRPV1 agonists in the tumor microenvironment without triggering other potentially harmful TRPV1-mediated reflex responses, such as the pulmonary chemoreflex [105].

This problem may be circumvented by identifying the substance produced by capsaicin-sensitive neurons that controls the metastatic potential of cancer cells. Originally, CGRP has been implicated in this action, but subsequently no difference in intratumoral CGRP was detected between resiniferatoxin-treated and control animals [118]. The expression of

the substance P receptor (neurokinin receptor-1, NK1) on breast cancer cells is, however, well documented [113]. In fact, substance P antagonism is emerging as a novel therapeutic option in patients with triple negative breast cancer [119].

A potentially even bigger problem is that the negative control of capsaicin-sensitive afferents on cancer growth and metastasis may be cancer-specific. In Walker tumor-bearing rats, capsaicin desensitization (intraperitoneal administration at a dose of 5 mg/kg for 13 days) decreased tumor growth by almost 50% [120]. Furthermore, in a mouse model of pancreatic ductal adenocarcinoma, ablation by neonatal capsaicin treatment of sensitive neurons delayed the formation of PaIN (pancreatic intraepithelial neoplasia), a precursor to carcinoma [121]. Authors speculated that it is the neurogenic inflammation that drives (presumably *via* Kras activation) the tumor initiation and progression in these animals [121].

Last, ablation by intrathecal capsaicin of sensory neurons had not effect on the growth of human oral squamous cell carcinoma transplanted into the paw of athymic mice [122].

In summary, defunctionalization of capsaicin-sensitive afferents may protect against pancreatic adenocarcinoma [121]; accelerate metastatic disease in breast carcinoma [116]; and have no effect on squamous cell carcinoma [122]. Since systemic desensitization of capsaicin-sensitive afferents in patients is not an option, this is of academic importance only. Local desensitization by high-dose capsaicin patches is possible; the growth of squamous cell carcinoma is, however, not affected by the absence of capsaicin-sensitive innervation [122].

The capsaicin receptor TRPV1 in cancer cells: Therapeutic target, diagnostic marker, or prognostic significance?

Capsaicin-sensitivity is a hallmark of a specific subdivision of peripheral sensory neurons [55,56]. These neurons express the capsaicin receptor TRPV1 at high levels. TRPV1 is, however, also expressed, albeit at comparatively very low levels, in non-neuronal cells, ranging from keratinocytes [123] through vascular endothelium [124] to immune cells [125]. The functional significance of this non-neuronal TRPV1 expression remains largely unclear. Although there is a plethora of papers on this subject, very few demonstrate the combined presence of TRPV1 mRNA, TRPV1 protein, and capsaicin-evoked responses blocked by TRPV1 antagonists in the same cell type. Indeed, the phenotype of animals desensitized to capsaicin reflect the absence of functioning sensory nerves (e.g. impaired noxious heat detection), but provides no clues about the physiological role of non-neuronal TRPV1 [126]. This is also true for the TRPV1 null mouse [127,128].

As already mentioned above, only those cancers represent a therapeutic target for TRPV1 agonists that are amenable to topical therapy, since systemic high-dose capsaicin administration is not an option in humans. For example, the human esophageal squamous cell carcinoma cell line ESCC expresses functional TRPV1, activated both by capsaicin (with an ED_{50} of 20.3 μM) and heat (44°C) [129]. Importantly, these responses were prevented by the TRPV1 antagonist, AMG-9810. There is preliminary evidence that oral and nasopharyngeal squamous cell carcinoma cells may also express functional TRPV1 [130,131]. Capsaicin may complement surgery and/or radiotherapy in the management of these tumors.

TRPV1 is the founding member of the group of heat-sensitive TRP channels, the so-called "thermoTRPs" [58,132]. The heat activation threshold of TRPV1, 41°C, is close to the temperature (42°C) that modulated electro-hyperthermia employs to kill tumor cells [133]. One can speculate that TRPV1 expressed on cancer cells is a target for modulated electro- hyperthermia.

An ideal diagnostic marker should be present in the cancer cell and absent in its benign counterpart or vice versa. For example, BCL2 is overexpressed in follicular lymphoma cells, but is absent in normal centrocytes. Relative changes in protein expression is more difficult to interpret. The literature on TRPV1 expression in various cancers is confusing. In human melanoma, one group described decreased TRPV1 expression compared to benign nevi [134] whereas another group reported the opposite result [135]. In human gastric adenocarcinoma decreased TRPV1 expression was found compared to surrounding normal mucosa [136], but it is normally not a diagnostic

challenge to differentiate gastrointestinal carcinoma from normal mucosa.

In a study of 33 patients with breast carcinoma, two patterns of TRPV1 expression was described: a classical membrane expression pattern, and a non-classical pattern with protein aggregates in endoplasmic reticulum and Golgi [137]. Patients with non-classical TRPV1 staining pattern did worse [137]. This is interesting academic research, but hardly useful for everyday practice.

A recent study examined the expression landscape of all the 27 TRP channel genes including *TRPV1* in 14 types of human cancers, ranging from bladder to uterus, using the International Cancer Genome Consortium database [88]. This database includes 4,854 human tumor samples along with 552 matched tissue controls. In most cancers examined, no change was found in *TRPV1* gene expression compared to control tissue (Table 1). Exception included lung adenocarcinoma (1.9-fold increase in *TRPV1* gene expression) and renal clear cell carcinoma (decreased expression, 0.673 compared to normal kidney). These changes are modest at best. For comparison, *TRPA1* gene expression shows a 28.7-fold increase over control in renal clear cell carcinoma.

Of course, changes in gene expression do not necessarily translate into altered protein expression. For instance, in hepatocellular carcinoma increased TRPV1 mRNA and protein levels were found [46] despite the lack of change (0.958 relative expression) in *TRPV1* gene expression [88].

Discussion

The literature on capsaicin and cancer is vast. A search of PubMed with these keywords has identified 876 papers, including a large number (152) of reviews. The internet also contains less scholarly articles on the health benefits [138] (or, conversely, deleterious effects [139]) of consuming hot, spicy food.

Unfortunately, the literature on capsaicin and cancer is confusing with different groups reporting exactly the opposite results. From this large body of literature, only two conclusions can be drawn. First, dietary capsaicin in "restaurant-like doses" is most likely safe to eat, though extremely hot concoctions are better avoided. Second, topical capsaicin creams and patches probably carry no risk for skin cancer.

The clinical value of *per os* capsaicin to complement chemotherapy is still speculative. By contrast, there is good experimental evidence that in animal models of human cancers capsaicin-sensitive afferents can influence the growth and metastatic potential of tumors. This is a promising area of research, though it is still unclear how it can be exploited for therapeutic purposes. The same is true for TRPV1 expression by cancer cells. There is no doubt that capsaicin can kill cancer cells, but systemic capsaicin administration in patients is not an option. However, topical capsaicin may find a role in the medical management of patients with cancers amenable to local therapy, such as oral or nasopharyngeal squamous cell carcinoma.

Last, TRPV1 expression in human cancers is subject to intensive research. As yet, no change has been detected that can be used in the daily practice of cancer diagnosis and prognostication.

Disclosure statement

No potential conflict of interest was reported by the author(s).

List of abbreviations

TRPV1	transient receptor potential, vanilloid-1
DMH	1,2-dimethylhydrazine
PSA	prostate-specific antigen
DMBA	7,12-dimethylbenzanthracene
PMA	phorbol 12-myristate 13-acetate
TPA	12-O-tetradecanoylphorbol-13-acetate
SP	substance P
CGRP	calcitonin gene-related peptide
NK	natural killer cell

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